Paper No. 29

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte TED C.K. LEE

Appeal No. 2003-0528
Application No. 09/314,841

ON BRIEF

Before WINTERS, ADAMS and GREEN, Administrative Patent Judges.

ADAMS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on the appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1, 2, 4, 5, 7-22, 24-39, 41-54, which are all the claims pending in the application.

Claim 1 is illustrative of the subject matter on appeal and is reproduced below:

1. A reagent for determining prothrombin time, comprising:
a recombinant protein tissue factor containing a portion derived from rabbit brain; an amino acid stabilizer compound selected from the group consisting of beta, gamma, and delta amino acids, and precursors thereof; and wherein the reagent remains stable for at least about 2 weeks at a selected temperature without drying or lyophilization.

The references relied upon by the examiner are:

Schwinn et al. (Schwinn)	4,297,344	Oct. 27, 1981
Butler et al. (Butler)	5,358,853	Oct. 25, 1994
Prestrelski et al. (Prestrelski)	5,580,856	Dec. 3, 1996
Hawkins et al. (Hawkins)	5,625,036	Apr. 29, 1997
Hora et al. (Hora)	5,730,969	Mar. 24, 1998
Brown	5,314,695	May 24, 1994
Brucato, et al. (Brucato)	WO 98/48283	Oct. 29, 1998

Mimms et al. (Mimms), "Phospholipid Vesicle Formation and Transmembrane Protein Incorporation Using Octyl Glucoside," Biochemistry, Vol. 20, pp. 833-840 (1981)

GROUNDS OF REJECTION

Claims 1, 2, 5, 7-11, 16-19, 21, 39, 43-45, 48-51, 53 and 54 stand rejected under 35 U.S.C. § 103 as being unpatentable over Brucato in view of Butler and Schwinn.

Claims 22, 29, 31, 32, 34, 35, 37 and 38 stand rejected under 35 U.S.C. § 103 as being unpatentable over Brown in view of Brucato, Butler and Schwinn.

Claims 12, 13, 41 and 42 stand rejected under 35 U.S.C. § 103 as being unpatentable over Brucato in view of Butler, Schwinn and Hawkins.

Claims 24 and 25 stand rejected under 35 U.S.C. § 103 as being unpatentable over Brown in view of Brucato, Butler, Schwinn and Hawkins.

Claims 4, 20, 26, 33, 36 and 52 stand rejected under 35 U.S.C. § 103 as being unpatentable over Brucato in view of Butler, Schwinn and Prestrelski with or without Brown.

Claims 14, 15, 27, 28, 46 and 47 stand rejected under 35 U.S.C. § 103 as being unpatentable over Brucato in view of Butler, Schwinn and Hora with or without Brown.

Claim 30 stands rejected under 35 U.S.C. § 103 as being unpatentable over Brown in view of Brucato, Butler, Schwinn, Prestrelski and Mimms.

We reverse.

DISCUSSION

Brucato in view of Butler and Schwinn:

According to the examiner (Answer, page 4), Brucato disclose "a reagent and method of measuring prothrombin time by mixing the reagent with plasma (blood) wherein the reagent comprises rabbit rTF [(recombinant Tissue Factor)] … in a formulation buffer comprising glycine (an amino acid stabilizer/chelating agent), BSA (carrier protein), PEG (humectant), calcium chloride, propionic acid, and antimicrobial agents…." The examiner recognizes, however, that Brucato does not teach a "beta, delta, or gamma amino acid stabilizer." Id. The examiner relies on Schwinn to make up for this deficiency in Brucato. According to the examiner (id.), Schwinn disclose "that glycine, beta-alanine, and GABA can be used as stabilizers for proteins, specifically coagulation factors…." The examiner relies on Butler to teach "that liquid prothrombin reagents comprising rabbit thromboplastin (also called tissue factor), calcium gluconate, BSA, a propionic salt, sodium chloride, and antimicrobials are stable for at least 14 days (2 weeks) and up to 20 months…." Id.

Based on this evidence the examiner concludes (Answer, bridging paragraph, pages 4-5):

> It would have been [prima facie] obvious to one of ordinary skill in the art at the time of the invention to formulate the liquid prothrombin reagent of B[rucato] to be stable for at least 2 weeks, as taught by B[utler], where the motivation would have been make

> [sic] a convenient, stable, and reliable liquid thromboplastin reagent with a long shelf life which avoids the turbidity and other problems inherent to a lyophilized product, as taught by B[utler]….

According to the examiner (Answer, page 5), "[o]ne skilled in the art would also would have expected success in formulating the liquid reagent of B[rucato] to be stable for at least two weeks, as taught by B[utler], because B[utler] teaches that a liquid reagent comprising rabbit thromboplastin, PEG, calcium gluconate, a propionate salt, BSA, and antimicrobial agents can be formulated to be stable for up to 20 months … and B[rucato]'s liquid reagent comprises a rabbit thromboplastin, PEG, calcium gluconate, propionic acid (i.e. propionate salt), BSA, and antimicrobial agents, as set forth above." In addition, the examiner concludes (Answer, page 6):

> It also would have been obvious to one of ordinary skill in the art at the time of invention to have used the beta alanine or GABA of S[chwinn] as stabilizers in the reagent of B[rucato] and B[utler] where the motivation would have been to use any amino acid known to be useful for stabilizing coagulation factor proteins (e.g. the thromboplastin of B[rucato]), as suggested by S[chwinn]'s teaching for a variety of amino acids to be used as coagulation factor stabilizers.

Upon consideration of this record, we cannot agree with the examiner's conclusion of obviousness. According to Butler (column 1, lines 33-37), "[t]he sensitivity of a thromboplastin reagent rests on a number of factors, such as the final reagent composition, which may include buffers, salts and stabilizers; the method of extracting the thromboplastin from tissue; and the original source of the tissue."

Butler's invention "is a liquid thromboplastin reagent composed of thromboplastin tissue extract, calcium ions, stabilizers and antimicrobials. This

reagent has a shelf life, in the unopened final container, of at least 16 months and once opened, of at least 10 days." Butler, (column 2, lines 38-42). Butler also discloses the effect of each component of the liquid thromboplastin reagent. See (column 5, line 32, to column 9, line 3). For example, Butler disclose (column 5, lines 41-43), "[t]he level of calcium has a minor role in the yield obtained, but has a dramatic effect on the normal range and the sensitivity of the resulting thromboplastin. Calcium gluconate provides the necessary calcium for the coagulation cascade that results in the formation of a clot." Butler's Table 2 (column 9) sets forth the preferred final concentrations of all thromboplastin reagent components. According to Butler (column 9, lines 35-40), "[a]s shown in Table 2, the components of the final formulation are calcium gluconate, sodium citrate, sodium chloride, PEG-1450, bovine serum albumin, sodium propionate and RBAP [rabbit brain acetone powder, the thromboplastin source] extract … [and] a combination of four antimicrobial compounds."

Recognizing that Butler discloses that the sensitivity of a thromboplastin reagent rests on a number of factors including final reagent composition, and that Butler's "reagent" has a shelf life of at least 16 months, we note that the examiner appreciates (Answer, page 4), that Brucato's reagent differs from the

reagent disclosed by Butler.[1] The examiner, however, blurs this distinction finding (Answer, page 5), both Brucato and Butler teach a liquid reagent comprising thromboplastin, "PEG, calcium gluconate, a propionate salt, BSA, and antimicrobial agents…." We find no reference to calcium gluconate in Brucato, and the examiner failed to identify where calcium gluconate is taught in Brucato.

The examiner also failed to appreciate that while Brucato teaches the presence of glycine in the liquid thromboplastin formulation Butler does not. Cf. Brucato, (page 14, line 5) with Butler, (Table 2). To the contrary, Butler's only mention of glycine is in regard to what can at best be read as an optional further processing step in the extraction of thromboplastin from tissues, and then only with a note of caution. According to Butler (column 2, lines 2-5), "[t]his [thromboplastin] extract can be further processed. For example, calcium lactate, glycine, carboxymethylcellulose and imidazole can be added to the thromboplastin extract. Each additive has an effect on the sensitivity of the reagent."

Notwithstanding the differences between Brucato and Butler discussed above, the examiner further blurs the distinction between Brucato and Butler by relying on Brown (a reference that is not part of this ground of rejection).

[1] According to the examiner (Answer, page 4), Brucato disclose a reagent comprising "rabbit rTF and synthetic phospholipids in a formulation buffer comprising glycine, BSA, PEG, calcium chloride, propionic acid, and antimicrobial agents. In contrast, the examiner finds (id.) Butler discloses "liquid prothrombin reagents comprising rabbit thromboplastin …, calcium gluconate, BSA, a propionic salt, sodium chloride, and antimicrobials…."

According to the examiner (Answer, page 6), "[o]ne skilled in the art would reasonably have expected success in using the beta alanine or GABA as stabilizers in the reagent of B[rucato] and B[rown] because both B[rucato] and B[rown] teach addition of glycine in their formulations and S[chwinn] teaches that beta alanine and GABA are equivalent stabilizers to glycine." However, as we understand the Butler patent, in contrast to using glycine as a stabilizer, Butler uses PEG, albumin and sodium propionate as stabilizers. Butler, (column 6, lines 48-52).

In our opinion, the examiner has not provided any evidence that beta alanine and GABA are equivalent stabilizers to PEG, albumin and sodium propionate, as set forth in Butler. To this end, the examiner has not provided any evidence to suggest that there would have been a reasonable expectation of success in modifying the Butler formulation, while retaining Butler's enhanced shelf life.

Furthermore, as appellants point out (Brief, bridging paragraph, pages 37-38), Schwinn (column 3, lines 45-50) is directed to blood coagulation factors II, VIII, XIII, of antithrombin III and of plasminogen and "a process for stabilizing coagulation factors against heat to prevent the transmission of hepatitis…. [T]he process for the stabilization against heat includes 'adding to the solution both an amino acid and a monosaccharide, an oligosaccharide or a sugar alcohol.'" Even if it were prima facia obvious to a person of ordinary skill in the art to modify Butler's reagent to include beta alanine or GABA, according to Schwinn one would also include a monocaccharide, oligosaccharide or a sugar alcohol.

Once again the examiner has failed to provide any factual evidence to support her position that modifying Butler's reagent in to include both glycine and a mono-, or oligo-saccharide, or a sugar alcohol would retain Butler's enhanced shelf life. In this regard, we remind the examiner that "it is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art." In re Wesslau, 353 F.2d 238, 241, 147 USPQ 391, 393 (CCPA 1965); see also In re Mercer, 515 F.2d 1161, 1165-66, 185 USPQ 774, 778 (CCPA 1975).

We recognize the examiner's statement (Answer, page 16), "[a]ppellant [sic] does not provide any reasons why one skilled in the art would NOT have expected success in using beta alanine or GABA as stabilizers in a tissue factor reagent; nor has appellant provided any evidence that GABA or beta alanine unexpectedly provide BETTER stability than the glycine of B[rucato] or B[utler]." In our opinion, the examiner has improperly attempted to shift her burden of establishing a prima facie case of obviousness to appellant. "In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. Only if that burden is met, does the burden of going forward with evidence or argument shift to the applicant." In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). Furthermore, we note that in order to establish a prima facie case of obviousness, there must be both some suggestion or motivation to modify the references or combine

reference teachings and a reasonable expectation of success. In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

As discussed above, the tissue factor formulations of Brucato and Butler are different. In addition, while Butler carefully explains the effect of each ingredient in their formulation having a shelf life of at least 16 months, Brucato makes no mention of a particular shelf life for their formulation. Accordingly, it is unclear if changes to the Butler formulation will result in a change in the shelf life of the formulation. Similarly, while Schwinn discloses that beta alanine and GABA can increase the heat stability of certain proteins it remains unclear what effect beta alanine and GABA will have on the shelf life of the formulation set forth in either of Brucato or Butler. While a person of ordinary skill in the art may possess the requisite knowledge and ability to modify the protocol taught by Brucato or Butler, the modification is not obvious unless the prior art suggested the desirability of the modification. In re Gordon, 733 F.2d 900, 902, 211 USPQ 1125, 1127 (Fed. Cir. 1984). Here we see no such reason to modify the references as applied.

Accordingly, for the reasons discussed above, we reverse the rejection of claims 1, 2, 5, 7-11, 16-19, 21, 39, 43-45, 48-51, 53 and 54 under 35 U.S.C. § 103 as being unpatentable over Brucato in view of Butler and Schwinn.

Brown in view of Brucato, Butler and Schwinn:

Brucato, Butler and Schwinn are relied upon as set forth above. The examiner relies (Answer, page 7) upon Brown to teach “a method of preparing a prothrombin reagent wherein lipids mixed with an antioxidant (BHT) are

redissolved in a solution comprising octyl-beta-D-glucopyranoside (octyl glucoside), glycine … rTF and a carrier protein…." The examiner recognizes, however, that Brown "does not teach[, inter alia,] stability of his reagent for at least two weeks at a selected temperature, nor does B[rown] teach a beta, delta or gamma amino acid stabilizer." Answer, page 7. Nevertheless, the examiner concludes (Answer, page 8),

> it would have been obvious to have included the incubation of phospholipids with rTF, as taught by B[rucato], in the method of B[rown], where the motivation would have been to maximize rTF incorporation into lipid micelles, as taught by B[rucato]. It would further have been obvious to have formulated the prothrombin reagent in the method of B[rown] in view of B[rucator] as a liquid with a stability of at least two weeks, as taught by B[utler], where the motivation would have been to make a convenient, stable, and reliable thromboplastin reagent with a long shelf life … as taught by B[utler]….

However, as discussed, supra, the examiner has not provided the evidence necessary to demonstrate that the Brucato, Butler or Brown prothrombin reagents could be modified in a manner that would retain shelf life as disclosed by Butler. Accordingly, we reverse the rejection of claims 22, 29, 31, 32, 34, 35, 37 and 38 under 35 U.S.C. § 103 as being unpatentable over Brown in view of Brucato, Butler and Schwinn.

Brucato in view of Butler, Schwinn and Hawkins with or without Brown:

Brucato, Butler, Brown and Schwinn are relied upon as set forth above. The examiner recognizes, however, that Brucato, Butler, Brown and Schwinn do not teach POPC or POPS. To make up for this deficiency, the examiner relies upon Hawkins. According to the examiner (Answer, page 10), Hawkins teach "a prothrombin reagent comprising rTF, POPS, and POPC…." Based on this

evidence (id.), the examiner concludes "[o]ne skilled in the art would reasonably have expected success in using POPC and POPS as the synthetic phospholipids in the reagent and methods of B[rucato], B[utler] and S[chwinn] or B[rown], B[rucato], B[utler], and S[chwinn]] because H[awkins] teaches that POPS and POPS [sic] can be combined with rTF in a method similar to that taught by B[rown]…."

However, as discussed, supra, the examiner has not provided the evidence necessary to demonstrate that the Brucato, Butler, Brown, or Hawkins prothrombin reagents could be modified in a manner that would retain shelf life as disclosed by Butler. Accordingly, we reverse the rejection of claims 12, 13, 41 and 42 stand rejected under 35 U.S.C. § 103 as being unpatentable over Brucato in view of Butler, Schwinn and Hawkins. For the same reason, we reverse the rejection of claims 24 and 25 stand rejected under 35 U.S.C. § 103 as being unpatentable over Brown in view of Brucato, Butler, Schwinn and Hawkins.

Brucato in view of Butler, Schwinn and Prestrelski with or without Brown:

Brucato, Butler, Brown and Schwinn are relied upon as set forth above. The examiner recognizes, however, that Brucato, Butler, Brown and Schwinn do not teach reagents dried at a selected temperature and humidity, which are not lyophilized. To make up for this deficiency the examiner relies on Prestrelski. According to the examiner (Answer, page 11), Prestrelski teach "air-drying of proteins at ambient temperature (about 20 [°]C) at low humidity….." The examiner further notes (id.), Prestrelski teach "that excipients such as alanine,

serine, glycerol, and sorbitol may be added to a protein formulation to improve storage stability…."

While the examiner points to the background section of Prestrelski to support her finding that alanine, serine, glycerol and sorbitol may improve storage stability of protein formulations, we note that the examiner has selected these excipients from a very large genus of excipients. See, Prestrelski, column 2, lines 4-18. The examiner has not identified any basis for identifying a select few of the excipients from the large genus listed. Furthermore, Prestrelski cautions against the use of additives (see Prestrelski, column 2, lines 19-23), "[w]hile the use of additives has improved the stability of dried proteins, many proteins which are subject to drying and subsequent storage contain unacceptable or undesirable amounts of inactive, aggregated protein in the rehydrated formulation." Thus, Prestrelski's acknowledgement of the problem of using additives for dried/lyophilized proteins only adds to the list of problems associated with lyophilized proteins identified by Butler. See, Butler, (column 1, lines 48-57).

As discussed, supra, the examiner has not provided the evidence necessary to demonstrate that the Brucato, Butler, or Brown prothrombin reagents could be modified in a manner that would retain shelf life disclosed by Butler. In our opinion, Prestrelski fails to make up for the deficiencies in the combination of Brucato, Butler and Schwinn with or without Brown. Accordingly, we reverse the rejection of claims 4, 20, 26, 33, 36 and 52 under 35 U.S.C.

§ 103 as being unpatentable over Brucato in view of Butler, Schwinn and Prestrelski with or without Brown.

Brucato in view of Butler, Schwinn and Hora with or without Brown:

Brucato, Butler, Brown and Schwinn are relied upon as set forth above. The examiner recognizes, however, that Brucato, Butler, Brown and Schwinn do not teach an aldehyde free polymeric carbohydrate, specifically gamma cyclodextrin. Answer, page 13. To make up for this deficiency the examiner relies on Hora. According to the examiner (id.), Hora teach "alpha, beta, or gamma cyclodextrins, and derivatives, can be used to stabilize both liquid and dried polypeptide formulations … and to protect against enzymatic hydrolysis…."

As discussed, supra, the examiner has not provided the evidence necessary to demonstrate that the Brucato, Butler, or Brown prothrombin reagents could be modified in a manner that would retain shelf life as disclosed by Butler. In our opinion, Hora fails to make up for the deficiency in Brucato, Butler and Schwinn, with or without Brown. Therefore, we reverse the rejection of claims 14, 15, 27, 28, 46 and 47 under 35 U.S.C. § 103 as being unpatentable over Brucato in view of Butler, Schwinn and Hora with or without Brown.

Brown in view of Brucato, Butler, Schwinn, Prestrelski and Mimms:

Brucato, Butler, Brown, Schwinn and Prestrelski are relied upon as set forth above. According to the examiner (Answer, page 14), the combination of Brucato, Butler, Brown, Schwinn and Prestrelski "do not teach multiple dialysis steps or dialysis against a buffer comprising serine." Therefore, the examiner relies upon Mimms. According to the examiner (id.), Mimms teach "dialysis of

phospholipid vesicles to remove detergents wherein the vesicles are dialyzed against two changes of buffer in order to trap different salts in the vesicles…."

As discussed, supra, the examiner has not provided the evidence necessary to demonstrate that the Brucato, Butler, or Brown prothrombin reagents could be modified in a manner that would retain shelf life as disclosed by Butler. In our opinion, Mimms fails to make up for the deficiency in Brucato, Butler, Brown, Schwinn and Prestrelski. Therefore, we reverse the rejection of claim 30 under 35 U.S.C. § 103 as being unpatentable over Brown in view of Brucato, Butler, Schwinn, Prestrelski and Mimms.

REVERSED

Sherman D. Winters Administrative Patent Judge	)
Donald E. Adams Administrative Patent Judge	) BOARD OF PATENT) APPEALS AND) INTERFERENCES
Lora M. Green Administrative Patent Judge	)

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